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Mini review

Maternal arsenic exposure and birth outcomes: A comprehensive review of the epidemiologic literature focused on drinking water

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ABSTRACT

Inorganic arsenic (iAs) is a human toxicant to which populations may be exposed through consumption of geogenically contaminated groundwater. A growing body of experimental literature corroborates the reproductive toxicity of iAs; however, the results of human studies are inconsistent. Therefore, we conducted a comprehensive review of epidemiologic studies focused on drinking water iAs exposure and birth outcomes to assess the evidence for causality and to make recommendations for future study. We reviewed 18 English language papers assessing birth weight, gestational age, and birth size. Thirteen of the studies were conducted among populations with frequent exposure to high-level groundwater iAs contamination (>10 μg/L) and five studies were conducted in areas without recognized contamination. Most studies comprised small samples and used cross-sectional designs, often with ecologic exposure assessment strategies, although several large prospective investigations and studies with individual-level measurements were also reported. We conclude that: (1) the epidemiologic evidence for an increased risk of low birth weight (<2500 g) is insufficient, although there exists limited evidence for birth weight decreases; (2) the evidence for increased preterm delivery is insufficient; and, (3) there exists minimal evidence for decreased birth size. In further investigation of birth weight and size, we recommend incorporation of individual susceptibility measures using appropriate biomarkers, with collection timed to windows of vulnerability and speciated arsenic analysis, as well as consideration of populations exposed primarily to drinking water iAs contamination <10 μg/L. Given the large potential public health impact, additional, high quality epidemiologic studies are necessary to more definitively assess the risk.

Introduction

The extensive distribution of inorganic arsenic (iAs) in the earth's crust leads to local and regional contamination of ground drinking water supplies and widespread human exposure (Amini et al., 2008; Smedley and Kinniburgh, 2002). Inorganic arsenic is well-absorbed by the mammalian gastrointestinal tract and numerous adverse health effects have been described in association with long-term exposure to concentrations >10 μg/L (Naujokas et al., 2013). In so-called 'arsenic endemic' regions, drinking water is often contaminated by >10 μg/L iAs and frequently higher than 50 μg/L iAs, including areas of Bangladesh, West Bengal India, Taiwan, Northern Chile, and Central and Eastern Europe (Smedley and Kinniburgh, 2002). However, exposure to drinking water sources contaminated primarily by <10 μg/L iAs is more widespread (Amini et al., 2008), and may also pose health risks. The World Health Organization and other regulatory bodies have set a maximum contaminant limit (MCL) of 10 μg/L iAs in drinking water for the protection of human health predicated on reducing cancer risk (WHO, 2004), yet this limit does not account for non-cancer endpoints, such as reproductive effects.

Concern is growing with respect to an increased risk for adverse birth outcomes associated with chronic drinking water iAs exposure, including lower birth weight, earlier delivery and smaller neonatal size in exposed mothers and their fetuses (Vahter, 2009). Previously, we reviewed the epidemiologic evidence for causal associations between drinking water iAs and pregnancy loss, and suggested that long-term exposure to iAs >10 μg/L increases the

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risk, but with a need for additional investigation into effect at <10 μg/L iAs (Bloom et al., 2010). Inorganic arsenic crosses the human placenta, and accumulates in the developing organs and systems of a fetus, posing an increased risk potential (Concha et al., 1998). A recent study reports detectable levels in newborn meconium (Vall et al., 2012). Experimental and observational evidence suggests that iAs accumulates in and disrupts placental function (Ahmed et al., 2011) and alters cord blood methylation (Pilsner et al., 2012).

Abnormal placentation is a strong risk factor for preterm delivery and restricted fetal growth (Murphy et al., 2006). Altered vasculogenesis leading to dysplastic placental development (He et al., 2007), modification of epigenetic markers (Tsang et al., 2012), and *in vitro* changes in placental levels of reactive oxygen species (Massrieh et al., 2006) have been reported following iAs treatment. Increased inflammatory processes were also reported for newborns exposed in utero via maternal consumption of iAs contaminated drinking water (Ahmed et al., 2011; Fry et al., 2007); inflammation is also a predictor of growth restriction and preterm delivery (Challis et al., 2009). Recently, a study of ultrasound measurements suggested restricted in utero growth with increased iAs exposure among male fetuses (Kippler et al., 2012). Studies have also demonstrated genotoxic (Chou et al., 2012) and anti-estrogenic (Davey et al., 2007) properties for iAs, as well as modified expression of genes associated with immune function (Andrew et al., 2008; Wu et al., 2003) and developmental processes (Andrew et al., 2008).

Adverse birth outcomes (WHO, 1977), including low birth weight (LBW; neonatal weight <2500 g at term) and preterm delivery (PD; live birth before 37 weeks completed gestation) are associated with a lifelong increased mortality risk (Crump et al., 2011). LBW and PD are also associated with an increased risk for various morbidities including neurodevelopmental disorders (Mwaniki et al., 2012), cardiovascular diseases and endocrine disorders (Barker, 2004). In 2010, approximately 11.1% of deliveries were preterm worldwide (Blencowe et al., 2012) and approximately 15% of newborns weighed <2500 g (UNICEF, 2012). Coupled to the widespread distribution of iAs contaminated drinking water, the high prevalence of LBW and PD makes even a modest increase in risk a significant global public health concern.

The animal evidence to date is controversial with respect to adverse birth outcomes and iAs exposure, primarily reporting associations at maternally toxic doses (Wang et al., 2006). Experimental studies, using high-dose intraperitoneal (Zirakjavanmard et al., 2011) or oral iAs treatment during gestation (Tsang et al., 2012), described decreased fetal or neonatal body weight or size. Low-dose iAs administration via drinking water to dams did not influence birth outcomes in one recent study, yet was associated with reduced postnatal growth (Kozul-Horvath et al., 2012). Substantial inter-species differences in the rates of iAs methylation and excretion (Vahter, 1999) make extrapolation of animal results to humans tenuous, and underscores the need for epidemiologic investigation. In fact, humans are likely to be more sensitive to arsenic toxicity than experimental animals (Mead, 2005). Therefore, our aim was to comprehensively assess the epidemiologic literature published to date and to characterize the strength of the evidence for causal associations between drinking water iAs exposure and birth outcomes. We also provide recommendations for future investigations to address existing data gaps.

Methods

We searched the scholarly literature using SCOPUS, a comprehensive abstract and citation database of research literature, which indexes 20,000 peer-reviewed journals worldwide including Medline (http://www.info.sciverse.com/scopus/). Our initial search was limited to original human research articles published in the English language through August 27th, 2013. To identify candidate papers we used the keyword combinations: 1. “arsenic” AND “birth outcomes” (19 papers identified); 2. “arsenic” AND “birth weight” (38 papers identified); 3. “arsenic” AND “birth size” (12 papers identified); 4. “arsenic” AND “reproductive outcomes” (22 papers identified); and 5. “arsenic” AND “newborn outcomes” (24 papers identified). We manually searched reference lists in selected papers and also employed reference lists from review papers to identify one additional publication. Paper titles and abstracts were reviewed and retained if arsenic exposure via drinking water and birth weight, gestational age and/or birth size was a study hypothesis. On January 1st, 2014 we updated the search to include two papers in addition to 16 papers retained from the initial search.

For each study, we abstracted and summarized the location and population sampled, epidemiologic design, sample size, exposure and outcome assessment strategies, covariates considered and the magnitude and precision of effect estimates. These characteristics were used in a qualitative evaluation of each study and to assess the impact of the reported results. Larger, prospective studies and those using individual exposure assessment strategies were afforded greater consideration than smaller, cross-sectional studies and those using ecologic exposure assessment strategies. Furthermore, the timing and nature of individual exposure assessment strategies were considered. We expressed study results as prevalence proportion ratios (PPR), odds ratios (OR), or average change per unit increase of exposure (β) and corresponding 95% confidence intervals (95% CIs) or *P*-values, as reported by the authors. If possible, we used SAS v.9.3 (SAS Institute, Inc. Cary, NC, USA) to calculate the PPR and 95% CIs for studies that did not report measures of effect. The overall strength and consistency of associations and evidence for a temporal relation in which exposure clearly proceeded outcome were used to assess the evidence for causality and to make recommendations for future studies (Hill, 1965).

Results and discussion

We evaluated 16 peer-reviewed studies that addressed drinking water iAs and birth weight (Table 1), nine studies that captured gestational age (Table 2) and five studies that addressed birth size (Table 3). Many studies captured multiple endpoints and most were conducted among populations residing in the so-called ‘arsenic-endemic’ regions of India, Bangladesh, China, and Taiwan, where drinking water iAs contamination is high, widespread and well-known.

Epidemiologic studies in South Asia

India

Approximately 6,000,000 persons residing in the West Bengal region of the Ganga Plain in eastern India may be at risk for exposure to iAs in ground water at levels of <10–3200 μg/L (Nordstrom, 2002). Large scale contamination also occurs in other Ganga Plain India locales, including Bihar (Chakraborti et al., 2003). Yet, only three published cross-sectional studies assessed the impact on birth outcomes in India. This work was completed in the context of large drinking water surveys conducted in the West Bengal and Bihar regions, where women employed sources contaminated by <3 μg/L iAs to as much as 1474 μg/L iAs.

In a small study of 16 Bihari women reporting 64 pregnancies, increased LBW (PPR = 8.33, 95% CI = 1.03, 67.14; Table 1) and PD (PPR = 3.33. 95% CI = 0.92, 12.11; Table 2) were associated with the use of wells contaminated by 463–1025 μg/L iAs (Chakraborti et al., 2003). In contrast, no associations (PPR = 0.79 and 1.05, respectively) were reported in a small follow-up study of 18 Bengali